Patent
Attorney's Docket No. 03786-046

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**BOX:AF**
Stephen M. BOYLE et al.	)	Group Art Unit: 1645
Application No.: 09/692,623	)	Examiner: Jennifer E. Graser
Filed: October 20, 2000	)	Confirmation No.: 2200
For: AN OVER-EXPRESSING HOMOLOGOUS ANTIGEN VACCINE AND A METHOD OF MAKING THE SAME	)	

REPLY

4/19/2

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

NU claims 24-27 only 28-30 were NOT

In complete response to the Office Action mailed November 19, 2002, Applicants submit the following remarks.

As correctly stated in the Official Action, Claims 24-30 are pending in the present application. Claims 24-30 stand rejected.

Information Disclosure Statement

Applicants submit herewith copies of the documents cited in the Information Disclosure Statement filed July 29, 2002, for the Examiner's convenience. Applicants note that these documents were cited by an Examiner in two related divisional cases, which are now abandoned.

Allowable Subject Matter

Claims 24-30 are pending in the present application. However, in the outstanding Official Action, only claims 24-27 are listed in the rejection under 35 U.S.C. § 103(a). Moreover, none of the features of claims 28-30 are mentioned in this rejection. Applicants therefore request that the Examiner indicate whether claims 28-30 contain allowable subject matter.

Rejections Under 35 U.S.C. § 103(a)

Claims 24-27 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Kontinen et al. (WO 94/19571) and Highlander et al. (U.S. 6,180,112). The Examiner argues that Kontinen et al. disclose a method for enhancing the secretion of homologous and heterologous bacterial exoproteins, including the use of multicopy plasmids. Kontinen also allegedly discloses that these proteins may be used as vaccines and pharmaceuticals. The Examiner acknowledges that Kontinen et al. do not disclose the use of the overproducing bacteria *per se* as vaccines, but rather the use of the overexpressed protein products as vaccines. However, the Examiner argues that Highlander et al. disclose the use of whole cell vaccine compositions comprising recombinant avirulent *P. haemolytica* containing a strong leukotoxin promoter for homologous overexpression of a leukotoxin antigen. The Examiner argues Highlander et al. disclose the use of heterologous antigens in addition to the overexpressed homologous antigens and the use of an attenuated strain of a gram-negative bacteria. Thus, the Examiner concludes that it would have been obvious to use multicopy plasmids to introduce homologous and heterologous antigens into

attenuated or avirulent bacteria and administer the bacteria as a vaccine. This rejection is respectfully traversed.

In order to establish a case of *prima facie* obviousness under 35 U.S.C. § 103, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2142. Applicants respectfully submit that the Examiner has not met these criteria.

Independent claims 24 and 27 require a) extracting DNA from the pathogenic micro-organism, b) obtaining a gene encoding an antigen that stimulates protective immunity, c) inserting the antigen gene into a multicopy plasmid, d) transforming an attenuated or avirulent strain of the pathogenic microorganism, and e) administering an effective amount of the vaccine (attenuated or avirulent strain overexpressing the homologous antigen) to a vertebrate. Claim 27 further requires that the pathogenic micro-organism be a *Brucella* strain. Applicants respectfully submit that each and every one of these elements of the presently claimed invention are not found in the Kontinen et al. or Highlander et al. publications, either alone or in combination.

The Examiner admits that Kontinen et al. do not disclose the use of the over-producing bacterial strains as vaccines. *See* Office Action, page 4. Kontinen et al. merely disclose the overexpression of antigens which can be isolated and used themselves as vaccines, not the use of attenuated or avirulent strains overexpressing homologous antigens as vaccines. Kontinen et al. disclose a protein expression/secretion system. Specifically,

Kontinen et al. disclose a method of enhancing protein secretion by increasing the quantity of a component of the *Bacillus* export machinery, PrsA, as the capacity of the secretory apparatus is the limiting factor in protein secretion and production in gram-positive bacteria. *See* page 7, lines 24-28.

There is no focus anywhere in Kontinen on vaccination/immunization. Rather, Kontinen et al. provides a method for generating industrial amounts of secreted proteins, including enzymes.

Even if Kontinen suggests the use of the overexpressed secreted proteins isolated by this method as possible vaccines, there is no motivation to combine the Kontinen et al. publication with the Highlander et al. publication. Nowhere in the Kontinen et al. publication are attenuated or avirulent strains disclosed or suggested for use in overexpressing homologous antigens. Thus, the Kontinen et al. publication fails to disclose or suggest at least one element of the presently claimed invention and, therefore, cannot render the presently claimed invention obvious.

Additionally, given the purpose of Kontinen et al., *i.e.*, to mass-produce exoproteins, one skilled in the art would not be motivated to use attenuated or avirulent bacteria as in the presently claimed invention.

Kontinen et al. merely discloses or suggests the use of the overexpressed exoproteins themselves as vaccines. This is **not** the same as using the bacteria overexpressing the exoproteins as vaccines. Applicants direct the Examiner's attention to page 10, lines 12-14 of Kontinen which states, "[e]xoproteins of medical interest can also be produced. Such proteins include diagnostic antigens, proteins that can be used as

vaccines and pharmaceuticals." The present claims explicitly require that the attenuated or avirulent strain of microorganism overexpressing the homologous antigen be used as a vaccine. Kontinen et al. do not contemplate the use of a strain of microorganism overexpressing the exoproteins as vaccines, and thus do not teach or suggest the present invention.

Applicants also take exception to the Examiner's statement, "Kontinen et al. is almost so close to the claimed invention that it could almost be a 102(b)." [Official Action, page 6]. "Close" is not the standard of either anticipation or obviousness. Rather the reference or combination of references must disclose or suggest every element of the presently claimed invention. *See* 35 U.S.C. §§ 102 and 103 and M.P.E.P. §2142.

Highlander et al. do not remedy the deficiencies of the Kontinen et al. publication. The Examiner relies on Highlander et al. as disclosing the use of whole cell vaccines. However, Highlander et al. disclose the use of a plasmid overexpressing an activator of the leukotoxin antigen not an antigen, as in the presently claimed invention. The Examiner emphasizes that the transcriptional *activator* is introduced on a multicopy plasmid. *See* Official Action, page 7. This feature of Highlander et al. is *irrelevant* to the presently claimed invention. The present claims require the use of a multicopy plasmid of the antigen itself to produce overexpression, not an activator of the antigen.

Claim 25 also recites the co-expression of one or more heterologous antigens, which is not disclosed or suggested by Kontinen et al. or Highlander et al. Despite the Examiner's statement that Highlander et al. disclose "the use of additional heterologous

antigens" (Official Action, page 4), Highlander et al. do not disclose the **co-expression** of both homologous and heterologous antigens. Instead, Highlander et al. state:

> It is also contemplated that the vaccine composition of the present invention will be used in combination with other vaccine preparations. Thus, it is intended that the present invention encompass multivalent vaccines in which recombinant *Pasteurella haemolytica* is **used in conjunction** with non-*Pasteurella* antigens/immunogens, including but not limited to viruses (e.g., parainfluenza), fungi, and bacteria. It is also intended that the present invention encompass multivalent vaccines in which recombinant *P. haemolytica* inactive leukotoxin is included as a purified preparation and used in conjunction with other immunogens/antigens such as Pasteurella heamolytica immunogens/antigens and or immunogens/antigens from other organisms.

Col. 5, lines 8-21 (emphasis added). Thus, Highlander et al. do not disclose or suggest the heterologous expression of proteins in bacteria homologously overexpressing an antigen stimulating protective immunity, but merely discuss the possible administration of additional vaccine components in conjunction with the recombinant *P. haemolytica*.

Applicants respectfully submit that there is no motivation to combine the Highlander et al. publication with the Kontinen et al. publication as the Highlander et al. publication does not suggest any need to increase the secretory capacity of a gram-positive bacteria, which is the goal of the Kontinen et al. publication. Kontinen et al. highlight the differences between gram-positive and gram-negative secretory machinery due to differences in the cell wall of these two types of bacteria. *See* page 1, line 12 to page 2, line 11. The method of Kontinen et al. relies upon the overexpression of a component of the gram-positive secretion apparatus identified in *Bacillus*.

Moreover, Kontinen et al. specifically state that "secretion in gram-positive bacteria can be enhanced by increasing the amount of cellular PrsA protein, or functional homologue(s) thereof, in gram-positive hosts that express greater than wild-type amounts of exoproteins of interest." Page 5, lines 26-29 (emphasis added). Although Kontinen et al. suggest a number of different exoproteins may be expressed using this system, perhaps including the heterologous expression of gram-negative exoproteins, the system of Kontinen et al. still requires a gram-positive host. Thus, even assuming *arguendo* that the combination of these two publications contained all elements of the presently claimed invention, one skilled in the art would still not be motivated to combine these two publications.

Even if one skilled in the art attempted to overexpress the leukotoxin discussed in Highlander et al. (*i.e.*, heterologous expression) in the Kontinen et al. system, this does not result in the presently claimed invention, which requires homologous expression of an antigen that stimulates protective immunity against the bacteria performing the overexpression. Instead, one skilled in the art would merely obtain a gram-positive bacteria overexpressing PrsA and the inactive *P. haemolytica* leukotoxin or activator of the promoter of the inactive leukotoxin. This does not resemble the presently claimed invention.

Further, the Kontinen et al. and Highlander et al. publications do not contain any motivation to specifically use attenuated or avirulent bacteria that overexpress a homologous antigen via a multicopy plasmid containing the antigen as a vaccine itself. As Kontinen et al. do not discuss whole cell vaccines, there is no suggestion of the use of an

attenuated or avirulent strain of bacteria as a vaccine. Highlander et al. note that leukotoxin is the primary virulence factor in *P. haemolytica*. *See* Col. 3, lines 8-13. Thus, the attenuated or avirulent *P. haemolytica* described by Highlander et al. is the result of the inactivation of the leukotoxin, the main thrust of the Highlander et al. publication. *See, e.g.*, col. 8, lines 59-62. In contrast, the present invention utilizes an already attenuated or avirulent bacteria to homologously over-express an antigen.

The Examiner's comment that Applicants' arguments in the previous Reply concerning the references not teaching that their vaccines stimulate "protective immunity" is not commensurate in scope with the claimed invention are unclear. *See* Official Action, page 6. Step b) of claims 24 and 27 requires the identification of a gene encoding at least one antigen that is capable of stimulating protective immunity. Therefore, Applicants respectfully submit that the comments made in the previous Reply are pertinent to the scope of the claimed invention.

Independent Claim 27 encompasses a homologous expression vaccine of *Brucella*. Applicants respectfully submit that there is nothing in either the Kontinen et al. or Highlander et al. publications to suggest the use of Brucella in a homologous expression vaccine. As noted above, Kontinen et al. describe the use of a **gram-positive** enhanced secretory system to express a variety of exoproteins. Highlander et al. specifically discuss only *P. haemolytica*. Therefore, the Highlander et al. and Kontinen et al. publications fail to disclose or suggest an additional element of independent Claim 27.

Moreover, the presently claimed invention produces surprising results. That is, the vaccines of the presently claimed invention provide greater protection against disease than

vaccines of the same attenuated or avirulent pathogen that expresses wild-type levels of the same homologous antigen. This is neither disclosed or suggested by either the Kontinen et al. or Highlander et al. publications. Kontinen et al. do not discuss vaccination/immunization other than as one possible use of the purified protein produced by the expression system. Highlander et al. actually produce inactive leukotoxin and thus would not achieve the results of the presently claimed invention.

In summary, Applicants respectfully submit that neither the Kontinen et al. nor the Highlander et al. publications, either alone or in combination, disclose or suggest every element of independent Claims 24 and 27. Moreover, Applicants respectfully submit that there is no motivation to combine these two publications. Finally, the presently claimed invention produces surprising results. Accordingly, the Kontinen et al. and Highlander et al. publications cannot render the presently claimed invention obvious. Withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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